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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/564,474	11/20/2006	Robert Olivieri	002441.00186	9877

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EXAMINER	
TONGUE, LAKIA J	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/564,474	OLIVIERI ET AL.	
	Examiner	Art Unit	
	LAKIA J. TONGUE	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *17-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 January 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. In view of the Pre-Brief Appeal Conference decision filed on October 15, 2010, the finality of the previous office action has been withdrawn. Claims 1-23 are pending. Upon further consideration claim 8 and 16 have been added to the prosecuted claims. Claims 17-23 were previously withdrawn. Claims 1-16 are currently under examination.

Rejections Withdrawn

2. In view of Applicant's arguments, the rejection of claims 1-7, 9-12, 14 and 15 under 35 U.S.C. 102(e) as being anticipated by Zollinger et al. (U.S. Patent 6,558,677 B2) is withdrawn.

3. In view of Applicant's arguments, the rejection of claims 1-7 and 9-13 under 35 U.S.C. 102(e) as being anticipated by Granoff et al. (U.S. 2006/0029621) is withdrawn.

4. In view of Applicant's arguments, the rejection of claims 1-7 and 9-15 under 35 U.S.C. 102(e) as being anticipated by Berthet et al. (U.S. 2006/0204520 A1) is withdrawn.

New Grounds of Objection and Rejection

Claim Objections

5. Claim 1 is objected to because of the following informalities: on first sight the acronym "OMV" should be followed by "Outer Membrane Vesicle". Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-4 and 10-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Fukasawa et al. (Vaccine, 1999; 17: 2951-2958).

Claim 1 is drawn to a process for preparing bacterial OMVs comprising a step of ultrafiltration of a crude OMV preparation containing bacterial DNA prior to any ultracentrifugation or sterilization steps.

Fukasawa et al. disclose that OMVs were obtained from *N. meningitidis* serogroup B strain, N44/89 (B:4:P1.15) strain. Said bacteria were grown in 60 l of complete Catlin's medium. The cells were removed from the culture by tangential diafiltration, which was prior to any ultracentrifugation or sterilization steps. The filtrate was concentrated with a 300,000 Nominal molecular weight limit (NMWL) cut-off, which is expressed in kilodaltons and ultracentrifuged (see page 2952; 2.1). Absent evidence to the contrary, tangential diafiltration is ultrafiltration with tangential flow.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

> the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-7 and 10-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fukasawa et al. (Vaccine, 1999; 17: 2951-2958), and further in view of Berthet et al. (US 2006/0204520 A1; Filed: 2/8/02).

Independent claim 1 is drawn to a process for preparing bacterial OMVs comprising a step of ultrafiltration of a crude OMV preparation containing bacterial DNA prior to any ultracentrifugation or sterilization steps.

Dependent claim 5 is drawn to the process of claim 1, wherein the membrane used for ultrafiltration has a cut off of about 300kDA.

Dependent claim 6 is drawn to the process of claim 1, wherein the OMVs are sterilized after ultrafiltration.

Dependent claim 7 is drawn to the process of claim 1, wherein the sterilization is by filter sterilization.

Dependent claim 14 is drawn to the process of claim 1, wherein the *N. meningitidis* has one or more mutations to decrease or knockout expression of a gene product.

Dependent claim 15 is drawn to the process of claim 14, wherein the gene product is Cps, CtrA, CtrB, CtrC, CtrD, ExbB, ExbD, FrpB, GalE, HtrB, MsbB, LbpA, LbpB, LpxK, NMB0033, OpA, OpC, PhoP, PilC, PmrE, PmrF, PorA, PorB, rmpM, SiaA, SiaB, SiaC, SiaD, SynA, SynB, SynC, TbpA and/or TbpB.

Fukasawa et al. disclose that OMVs were obtained from *N. meningitidis* serogroup B strain, N44/89 (B:4:P1.15) strain. Said bacteria were grown in 60 l of

complete Catlin's medium. The cells were removed from the culture by tangential diafiltration, which was prior to any ultracentrifugation or sterilization steps. The filtrate was concentrated with a 300,000 Nominal molecular weight limit (NMWL) cut-off, which is expressed in kilodaltons and ultracentrifuged (see page 2952; 2.1). Absent evidence to the contrary, tangential diafiltration is ultrafiltration with tangential flow.

Fukasawa et al. do not specifically disclose that the membrane used for ultrafiltration has a cut off of about 300kDA as recited in claim 5; that the OMVs are sterilized after ultrafiltration as recited in claim 6; that the sterilization is by filter sterilization as recited in claim 7; that the *N. meningitidis* has one or more mutations to decrease or knockout expression of a gene product as recited in claim 14; or that the gene product is Cps, CtrA, CtrB, CtrC, CtrD, ExbB, ExbD, FrpB, GalE, HtrB, MsbB, LbpA, LbpB, LpxK, NMB0033, OpA, OpC, PhoP, PilC, PmrE, PmrF, PorA, PorB, rmpM, SiaA, SiaB, SiaC, SiaD, SynA, SynB, SynC, TbpA and/or TbpB as recited in claim 15.

Berthet et al. disclose a process for preparing bacterial OMV's of engineered Gram-negative bacterial strains that have improved outer-membrane vesicle shedding properties (see paragraph 0002). Berthet et al. disclose that vesicles prepared from such modified strains may have reduced particle size, which allows sterile filtration through 0.22 µm pores (see paragraph 0058). Moreover, Berthet et al. disclose that many bacterial outer membrane components are present such as PorA, PorB, Opc, Opa, FrpB and possess observed protection; others such as TbpB have been defined as being relevant to the induction of protective immunity (see paragraph 0013). Berthet et al. disclose that preferred Neisserial (particularly, Neisseria *meningitidis* B) vesicle

preparations include one or more preferred genes selected from PorA, PorB, PilC, ThpA, TbpB, LbpA, LbpB, Opa, and Opc or htrB, MsbB and lpxK for down regulation (see paragraphs 0091-93).

Limitations such as the cut off weight of the ultrafiltration membrane are being viewed as limitations of optimizing experimental parameters.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of Fukasawa et al. with the teachings of Berthet et al. to modify said *N. meningitidis* strain with one or more mutation to decrease or knockout expression of a gene product because purification of blebs is technically difficult; bleb production in most Gram-negative strains results in poor yields of product for the industrial production of vaccines. Therefore, modifying said strain solves this problem and provides specially modified “hyperblebbing” strains from which vesicles may be more easily made in higher yield and may be more homogeneous in nature. Said vesicles may then be readily filter sterilized. Additionally, if the bacteria produce more vesicles then the usual process steps to remove detergent such as purification and centrifugation may be obviated (see Berthet et al.; paragraphs 0036-0037). Moreover, it would be prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of Fukasawa et al. with the teachings of Berthet et al. to modify the specific genes as claimed because they are the most common genes of many bacterial outer membrane components.

Lastly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of Fukasawa et al. with the

teachings of Berthet et al. to sterilize the OMVs by filter sterilization because it utilizes a filter with smaller pores which will limit the amount of material that may become clogged along the process.

One would have had a reasonable expectation, barring evidence to the contrary, that the method would be effective for a process for preparing bacterial OMVs.

Since the claimed method steps were known in the prior art and one skilled in the art could have combined the steps as claimed by known methods with no change in their respective functions and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. See the recent Board decision *Ex parte Smith,--USPQ2d--,* slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing *KSR, 82 USPQ2d* at 1396).

8. Claims 1, 2, 4, 5, 8-13 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Granoff et al. (U.S. Patent 6,936,261 B2; Filed 7/27/01) and further in view of van Reis et al. (Current Opinion in Biotechnology, 2001; 12: 208-211).

Independent claim 1 is drawn to a process for preparing bacterial OMVs comprising a step of ultrafiltration of a crude OMV preparation containing bacterial DNA prior to any ultracentrifugation or sterilization steps.

Independent claim 16 is drawn to a process for purifying bacterial OMVs, wherein the process does not a centrifugation step in which the OMVs are pelleted.

Granoff et al. disclose compositions comprising OMV against diseases caused by *Neisseria meningitidis*, specifically serogroup B strains (see title and abstract).

Granoff et al. disclose a composition comprising outer membrane vesicles (OMV) prepared from the outer membrane of a cultured strain of Neisseria meningitidis spp. OMVs may be obtained from a Neisseria meningitidis grown in broth or solid medium culture, preferably by separating the bacterial cells from the culture medium by filtration, lysing the cells (e.g. by addition of detergent, osmotic shock, sonication, cavitation, homogenization, or the like) and separating an outer membrane fraction from cytoplasmic molecules by filtration; outer membrane fractions may be used to produce OMVs (see column 14, lines 19-35). Granoff et al. disclose that their experiments included outer membrane vesicle vaccine prepared from *N. meningitidis* serogroup B strain, H44/76 (B:15:P1.7,16; “Norwegian vaccine"), (see column 4, lines 7-14). Moreover, Granoff et al. disclose that the composition may include an adjuvant (see column 15, lines 18-22).

Granoff et al. do not specifically disclose the use of ultra filtration as recited in claim 1; that the ultrafiltration is cross flow or tangential flow as recited in claim 4; or that the membrane used for ultrafiltration has a cut off of about 300kDA as recited in claim 5.

van Reis et al. disclose membrane separations in biotechnology, which include microfiltration and ultrafiltration for protein concentration and buffer exchange. van Reis et al. disclose that ultrafiltration (UF) has become the method of choice for protein concentration and buffer exchange, largely replacing size-exclusion chromatography. UF devices have been developed in which the pressure, fluid flow, and concentration profiles remain constant when changing the scale of operation. Equal flow distribution among channels/fibers is achieved using appropriate piping manifolds and proper

design of entrance and exit regions. The system allows 1000-fold volumetric scaling of UF process with consistent protein yield and process flux. Moreover, a new control strategy in which concentration of retained protein at the membrane surface remains constant has been developed, which enables processes with enhanced product yield, minimal membrane area, consistent process time and greater robustness with respect to variations in feed quality and membrane properties (see page 209; Ultrafiltration). Tangential flow microfiltration using 0.2 µm-rated membranes generates a particle free harvest solution that requires no additional clarification before subsequent purification. The systems are operated at a constant flux instead of constant trans-membrane pressure to improve product yield and throughput (see page 208). van Reis et al. disclose that high performance tangential flow filtration (HPTFF) is an emerging technology for protein purification. It is a two-dimensional unit operation that exploits both size and charge mechanisms. Additionally, protein concentration, purification and buffer exchange can be accomplished in a single unit operation. HPTFF has equivalent throughput to UF (see page 209; High-performance tangential flow filtration).

With regard to claim 16, which requires that the process not include a centrifugation step in which the OMVs are pelleted, the process of Granoff discloses that separating an outer membrane fraction from cytoplasmic molecules can be done by filtration; *or* by differential precipitation *or* aggregation of outer membranes and/*or* outer membrane vesicles, *or* by affinity separation methods using ligands that specifically recognize outer membrane molecules; *or* by a high-speed centrifugation

that pellets outer membranes and/*or* outer membrane vesicles, or the like (see column 14, lines 27-35), which the Examiner is interpreting "or" as in an alternative option to the others listed. As such, the process of Granoff to exclude a centrifugation step in which the OMVs are pelleted is disclosed by Granoff.

Limitations such as the cut off weight of the ultrafiltration membrane are being viewed as limitations of optimizing experimental parameters.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of Granoff et al. with the ultrafiltration of van Reis et al. to prepare bacterial OMVs, comprising a step of ultrafiltration prior to any ultracentrifugation or sterilization steps because ultrafiltration membranes and process designs can provide the high concentration factors and greater overall yield required for high-dose products (see page 210; conclusions). Moreover, it would have been prima facie obvious to use ultrafiltration that is tangential flow because high performance tangential flow filtration (HPTFF) is a two-dimensional unit operation that exploits both size and charge mechanisms, is an emerging technology for protein purification, has equivalent throughput to ultrafiltration and is sufficient to accomplish protein concentration, purification and buffer exchange in a single unit operation.

One would have had a reasonable expectation, barring evidence to the contrary, that the method would be effective for a process for preparing bacterial OMVs.

Since the claimed method steps were known in the prior art and one skilled in the art could have combined the steps as claimed by known methods with no change in

their respective functions and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

9. Claims 6, 7, 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Granoff et al. (U.S. Patent 6,936,261 B2; Filed 7/27/01) and further in view of van Reis et al. (Current Opinion in Biotechnology, 2001; 12: 208-211) as applied to claims 1, 2, 4, 5, 8-13 and 16 above, and further in view of Berthet et al. (US 2006/0204520 A1; Filed: 2/8/02).

Independent claim 1 is drawn to a process for preparing bacterial OMVs comprising a step of ultrafiltration of a crude OMV preparation containing bacterial DNA prior to any ultracentrifugation or sterilization steps.

Dependent claim 6 is drawn to the process of claim 1, wherein the OMVs are sterilized after ultrafiltration.

Dependent claim 7 is drawn to the process of claim, wherein the sterilization is by filter sterilization.

Dependent claim 14 is drawn to the process of claim 1, wherein the *N. meningitidis* has one or more mutations to decrease or knockout expression of a gene product.

Dependent claim 15 is drawn to the process of claim 14, wherein the gene product is Cps, CtrA, CtrB, CtrC, CtrD, ExbB, ExbD, FrpB, GalE, HtrB, MsbB, LbpA, LbpB, LpxK, NMB0033, OpA, OpC, PhoP, PilC, PmrE, PmrF, PorA, PorB, rmpM, SiaA, SiaB, SiaC, SiaD, SynA, SynB, SynC, TbpA and/or TbpB.

The teachings of Granoff et al. have been described previously.

The teaching of van Reis et al. have been described previously.

Granoff et al. and van Reis et al. do not specifically disclose that the OMVs are sterilized after ultrafiltration as recited in claim 6; that the sterilization is by filter sterilization as recited in claim 7; that the *N. meningitidis* has one or more mutations to decrease or knockout expression of a gene product as recited in claim 14; or that the gene product is Cps, CtrA, CtrB, CtrC, CtrD, ExbB, ExbD, FrpB, GalE, HtrB, MsbB, LbpA, LbpB, LpxK, NMB0033, OpA, OpC, PhoP, PilC, PmrE, PmrF, PorA, PorB, rmpM, SiaA, SiaB, SiaC, SiaD, SynA, SynB, SynC, TbpA and/or TbpB as recited in claim 15.

Berthet et al. disclose a process for preparing bacterial OMV's of engineered Gram-negative bacterial strains that have improved outer-membrane vesicle shedding properties (see paragraph 0002). Berthet et al. disclose that vesicles prepared from such modified strains may have reduced particle size, which allows sterile filtration through 0.22 µm pores (see paragraph 0058). Moreover, Berthet et al. disclose that many bacterial outer membrane components are present such as PorA, PorB, Opc, Opa, FrpB and possess observed protection; others such as TbpB have been defined as being relevant to the induction of protective immunity (see paragraph 0013). Berthet et al. disclose that preferred Neisserial (particularly, Neisseria *meningitidis* B) vesicle preparations include one or more preferred genes selected from PorA, PorB, PilC, ThpA, TbpB, LbpA, LbpB, Opa, and Opc or htrB, MsbB and lpxK for down regulation (see paragraphs 0091-93).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of Granoff et al. and van Reis et al. as combined above, with the teachings of Berthet et al. to modify said strain with one or more mutation to decrease or knockout expression of a gene product because purification of blebs is technically difficult; bleb production in most Gram-negative strains results in poor yields of product for the industrial production of vaccines. Therefore, modifying said strain solves this problem and provides specially modified "hyperblebbing" strains from which vesicles may be more easily made in higher yield and may be more homogeneous in nature. Said vesicles may then be readily filter sterilized. Additionally, if the bacteria produce more vesicles then the usual process steps to remove detergent such as purification and centrifugation may be obviated (see Berthet et al.; paragraphs 0036-0037). Moreover, it would be prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of Granoff et al. and van Reis et al. with the teachings of Berthet et al. to modify the specific genes as claimed because they are the most common genes of many bacterial outer membrane components.

Lastly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of Granoff et al. and van Reis et al. with the teachings of Berthet et al. to sterilize the OMVs by filter sterilization because it utilizes a filter with smaller pores which will limit the amount of material that may become clogged along the process.

One would have had a reasonable expectation, barring evidence to the contrary, that the method would be effective for a process for preparing bacterial OMVs.

Since the claimed method steps were known in the prior art and one skilled in the art could have combined the steps as claimed by known methods with no change in their respective functions and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. See the recent Board decision *Ex parte Smith,--USPQ2d--,* slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing *KSR, 82 USPQ2d* at 1396).

Conclusion

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAKIA J. TONGUE whose telephone number is (571)272-2921. The examiner can normally be reached on Monday-Friday 8-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Patricia Duffy can be reached on 571-272-0855. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LJT
1/4/11

/Vanessa L. Ford/
Primary Examiner, Art Unit 1645